PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 471/04, A61K 31/435 // (C07D 471/04, 221:00, 221:00)

A1

(11) International Publication Number: WO 96/39406

(43) International Publication Date: 12 December 1996 (12.12.96)

(21) International Application Number: PCT/US95/07211

(22) International Filing Date: 6 June 1995 (06.06.95)

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

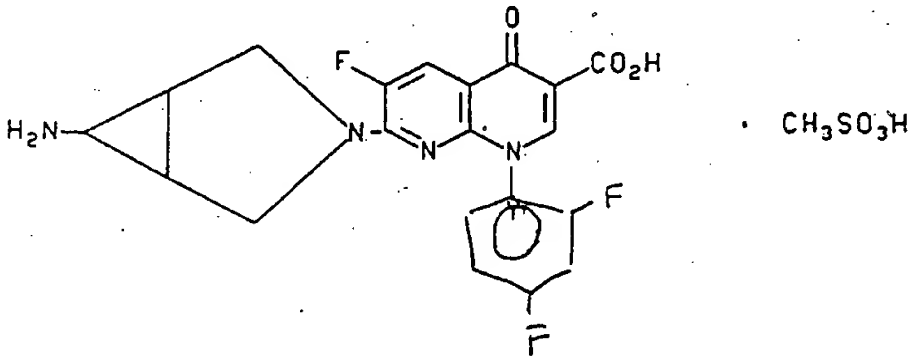
(75) Inventors/Applicants *(for US only)*: HANDANYAN, Lynne, A. [US/US]; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US). MORRIS, Thomas, A. [US/US]; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US). HENDRICKSON, Robert, L. [US/US]; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US). JOHNSON, Phillip, J. [US/US]; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US). NORRIS, Timothy [GB/US]; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: CA, FI, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NOVEL CRYSTAL FORM OF ANHYDROUS 7-([1α, 5α, 6α]-6-AMINO-3-AZABICYCLO[3.1.0]HEX-3-YL)-6-FLUORO-1-(2,4-DIFLUOROPHENYL)-1,4-DIHYDRO-4-OXO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID, METHANESULFONIC ACID SALT



(57) Abstract

The anhydrate of 7-([1α, 5α, 6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt has advantageous stability for formulation as an antibacterial agent.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

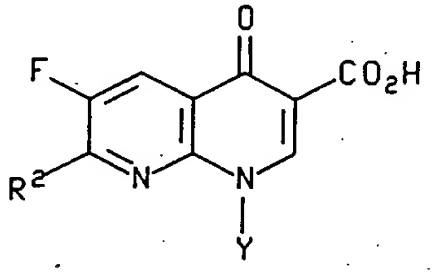
AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

NOVEL CRYSTAL FORM OF ANHYDROUS 7-([1α,5α,6α]-6-AMINO-3-AZABICYCLO[3.1.0]HEX-3-YL)-6-FLUORO-1-(2,4-DIFLUOROPHENYL)-1,4-DIHYDRO-4-OXO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID, METHANESULFONIC ACID SALT

Background of the Invention

The invention is directed to a novel crystal form of anhydrous 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, a method of using said compound in the treatment of a bacterial infection in mammals, especially humans, and to pharmaceutical compositions useful therefor.

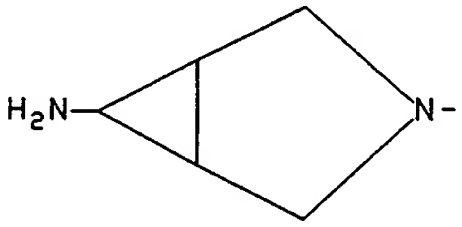
United States Patent No. 5,229,396, which is incorporated herein by reference, discloses 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt of the formula



· CH_3SO_3H

I

wherein Y is o,p-difluorophenyl and R^2 is



II

having antibacterial activity.

Summary of the Invention

The invention is directed to a novel crystal form of anhydrous 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt which possesses valuable and nonobvious properties. Since the anhydrate is substantially hydrophobically stable, formulation problems of the active ingredient during tableting or capsulation operations are alleviated.

Detailed Description of the Invention

The 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt referred to in United States Patent No. 5,229,396 characterized by the major peaks in the following X-ray powder diffraction pattern

Peak no.	1	2	3	4	5	6	7	8	9	10
2θ(°) Cu	5.0	9.8	13.0	14.8	19.7	20.9	22.0	23.0	28.1	29.3
d space	17.9	9.0	6.8	6.0	4.5	4.2	4.0	3.9	3.2	3.0

is substantially hygroscopic and can pick up water from the atmosphere to form a monohydrate. The monohydrate is characterized by the major peaks in the following X-ray powder diffraction pattern

Peak no.	1	2	3	4	5	6	7	8
2θ(°) Cu	4.7	9.4	12.4	13.1	13.6	14.2	17.0	17.9
d space	18.7	9.4	7.1	6.7	6.5	6.3	5.2	5.0
Peak no.	9	10	11	12	12	14	15	
2θ(°) Cu	18.7	21.0	22.0	24.2	24.2	26.6	27.2	
d space	4.7	4.2	4.0	3.7	3.7	3.5	3.3	

The novel crystal form of 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt (hereinafter "the anhydrate") is hydrophobically stable and characterized by the major peaks in the following X-ray powder diffraction pattern.

Peak no.	1	2	3	4	5	6	7	8
2θ(°) Cu	4.5	7.7	9.1	13.6	15.0	18.2	18.6	22.8
d space	19.5	11.5	9.7	6.5	5.9	4.9	4.8	3.9

The anhydrate may be prepared by heating 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its derived monohydrate in an organic solvent or a mixture thereof with an aprotic co-solvent, such as isopropanol, dimethylsulfoxide, n-propanol, tetrahydrofuran or n-butanol, preferably n-butanol or tetrahydrofuran/n-butanol, to reflux or to a temperature between about 70°C to about 90°C, preferably about 85°C. Depending on the reaction temperature and other conditions, the reaction time generally ranges from about 1 hour to about 20 hours, preferably about 2 hours to about 16 hours.

The crystal slurry formed is cooled to a temperature between about 20°C to about 30°C, preferably about 25°C, for a time period between about 2 hours to about 24 hours, preferably about 2 hours to about 12 hours. The crystalline product is then filtered from the mother liquid and dried under vacuum until all the solvent has been removed.

The anhydrate may be administered as an antibacterial agent as described in above-mentioned United States Patent No. 5,229,396. Administration to a subject may be alone, but the anhydrate will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, it can be administered orally or in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. In the case of animals, it is advantageously contained in an animal feed.

The invention also provides pharmaceutical compositions comprising an antibacterially effective amount of the anhydrate together with a pharmaceutically acceptable diluent or carrier.

The anhydrate can be administered to humans for the treatment of bacterial diseases by either the oral or parenteral routes, and may be administered orally at dosage levels of about 0.1 to 500 mg/kg/day, advantageously 0.5-50 mg/kg/day given

in a single dose or up to 3 divided doses. For intramuscular or intravenous administration, dosage levels are about 0.1-200 mg/kg/day, advantageously 0.5-50 mg/kg/day. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. Variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of administration chosen as will be known to those skilled in the art.

The antibacterial activity of the anhydrate is shown by testing according to the Steer's replicator technique which is a standard in vitro bacterial testing method described by E. Steers et al., Antibiotics and Chemotherapy, 9, 307 (1959).

The hydration properties were determined gravimetrically over a range of relative humidities using a VTI microbalance system for moisture sorption studies (Model MB300W).

PREPARATION A

7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt

7-([1α,5α,6α]-6-tert-butyloxycarbonylamino-3-azabicyclo]3,1.0]hex-3yl)-6-fluoro-1(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester, (25 g) and methanesulfonic acid (11 g) was added to a mixture of water (250 mL) and tetrahydrofuran (250 mL). The resultant slurry was heated to reflux (about 66°C) temperature and held at this temperature for 20 hours after which time a clear solution was obtained. The solution was cooled to 35-40°C and concentrated under reduced pressure to about half its original volume. The resultant crystal slurry was cooled slowly to room temperature (about 20°C) and then further stirred at 10°C for 2 hours. The crystalline product 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt was isolated by filtration and washed with a mixture of tetrahydrofuran (12.5 mL) and water (12.5 mL). The crystals were dried under vacuum at 30-35° until the residual water content of the crystals was below 0.2%. Yield 21.2 g, 90%.

The crystals of 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-

1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt are characterized by the major peaks in the following X-ray powder diffraction pattern.

Peak no.	1	2	3	4	5	6	7	8	9	10
2θ(°) Cu	5.0	9.8	13.0	14.8	19.7	20.9	22.0	23.0	28.1	29.3
d space	17.9	9.0	6.8	6.0	4.5	4.2	4.0	3.9	3.2	3.0

The crystals of 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt can pick up water from the atmosphere and form a monohydrate. The monohydrate is characterized by the major peaks in the following X-ray powder diffraction pattern.

Peak no.	1	2	3	4	5	6	7	8
2θ(°) Cu	4.7	9.4	12.4	13.1	13.6	14.2	17.0	17.9
d space	18.7	9.4	7.1	6.7	6.5	6.3	5.2	5.0
Peak no.	9	10	11	12	12	14	15	
2θ(°) Cu	18.7	21.0	22.0	24.2	24.2	26.6	27.2	
d space	4.7	4.2	4.0	3.7	3.7	3.5	3.3	

Example 1

7-([1α, 5α, 6α]-6-amino-3-azabicyclo[3.1.0]hex-3y)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, anhydrous

7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its monohydrate (20 g) was stirred with isopropanol (220 ml). The crystal suspension was refluxed for 16 hours or until microscopic examination had shown that the crystal form had changed to a hexagonal form. The crystal slurry was cooled to 20-25°C and stirred at this temperature for about 1 hour. The crystalline product was filtered from the mother liquor, washed with isopropanol (about 50 mL) and dried under vacuum at 40°C until all the solvent had been removed. Yield 98%.

The product is a new polymorphic form of 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, anhydrous, characterized by the following major peaks in its X-ray powder diffraction pattern.

Peak no.	1	2	3	4	5	6	7	8
2θ(°) Cu	4.5	7.7	9.1	13.6	15.0	18.2	18.6	22.8
d space	19.5	11.5	9.7	6.5	5.9	4.9	4.8	3.9

Example 2

7-([1α, 5α, 6α]-6-amino-3-azabicyclo[3.1.0]hex-3y)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, anhydrous

7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its monohydrate (7 g) was dissolved in dimethylsulfoxide, DMSO (21 mL) by heating to 80-85°C until complete solution was obtained. Isopropanol (150 mL) was added dropwise to the solution at about 85°C to induce crystallization. The crystal suspension was held at reflux temperature about 85°C for 2-16 hours or until microscopic examination had shown that the crystal form had changed to a hexagonal form. The resultant crystal slurry was cooled to 20-25°C. The crystalline product was filtered from the mother liquor, washed with isopropanol (about 50 mL) and dried under vacuum at 50°C until all the solvents had been removed. Yield 77%.

The product is the same as in Example 1.

Example 3

7-([1α, 5α, 6α]-6-amino-3-azabicyclo[3.1.0]hex-3y)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, anhydrous

7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its monohydrate (55.6 g) was dissolved in dimethylsulfoxide, DMSO (159 mL) by heating to 80-85°C until complete solution was obtained. The solution was cooled to 20-25°C and stirred for 2 hours until a crystal slurry formed. Dichloromethane (1200 mL) was

added dropwise to the solution at about 25°C to fully induce crystallization. The crystal suspension was held at room temperature overnight or until microscopic examination had shown that the crystal form had changed to a hexagonal form. The crystalline product was filtered from the mother liquor, washed with dichloromethane (3 x 119 mL) and dried under vacuum at 50°C until all the solvent had been removed. Yield 91%.

The product is the same as in Example 1.

Example 4

7-([1α, 5α, 6α]-6-amino-3-azabicyclo[3.1.0]hex-3y)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, anhydrous

7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its monohydrate (1 g) was stirred with n-propanol (44 mL). The crystal suspension was refluxed for 3 hours or until microscopic examination had shown that the crystal form had changed to a hexagonal form. The crystal slurry was cooled at 20-25°C and stirred overnight. The crystalline product was filtered from the mother liquor, washed with n-propanol (about 10 mL) and dried under vacuum at 50-55°C until all the solvent had been removed. Yield 68%.

The product is the same as in Example 1.

Example 5

7-([1α, 5α, 6α]-6-amino-3-azabicyclo[3.1.0]hex-3y)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, anhydrous

7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its monohydrate (70 g) was stirred with a mixture of tetrahydrofuran (175 mL) and a n-butanol (525 mL). The crystal suspension was heated for 16 hours or until microscopic examination had shown that the crystal form had changed to a hexagonal form. The crystal slurry was cooled to 20-25°C and stirred overnight. The crystalline product was filtered from the mother liquor, washed with a mixture of tetrahydrofuran (25 mL) and n-butanol (75 mL) and dried under vacuum at 80°C until all the solvent had been removed. Yield 95%.

The product is the same as in Example 1.

Example 6

7-([1α, 5α, 6α]-6-amino-3-azabicyclo[3.1.0]hex-3y)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt, anhydrous

7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its monohydrate (5 g) was stirred with n-butanol containing up to 1% water (220 mL). The crystal suspension was heated to reflux for 5 hours or until microscopic examination had shown that the crystal form had changed to a hexagonal form. The crystal slurry was cooled to 20-25°C and stirred overnight. The crystalline product was filtered from the mother liquor, washed with n-butanol (about 20 mL) and dried under vacuum at 50-55°C until all the solvent had been removed. Yield 92%.

The product is the same as in Example 1.

CLAIMS

1. 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt characterized by the following major peaks in its X-ray powder diffraction pattern

Peak no.	1	2	3	4	5	6	7	8
2θ(°) Cu	4.5	7.7	9.1	13.6	15.0	18.2	18.6	22.8
d space	19.5	11.5	9.7	6.5	5.9	4.9	4.8	3.9

2. A pharmaceutical composition having antibacterial activity comprising the compound according to claim 1 in an amount effective in the treatment of a bacterial infection, and a pharmaceutically acceptable carrier.

3. A method of treating a bacterial infection which comprises administering to a subject in need of treatment an antibacterial amount of the compound according to claim 1.

4. A process for preparing the compound according to claim 1, which comprises heating 7-([1α,5α,6α]-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, methanesulfonic acid salt or its derived monohydrate in the presence of an alcohol or mixture thereof with an aprotic co-solvent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/07211

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 //(C07D471/04,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 413 455 (PFIZER) 20 February 1991 see claim 11; example 13B & US,A,5 229 396 (BRIGHTY) cited in the application	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 1996	19. 02. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ..ational application No.
PCT/US95/07211

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 3 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/07211

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-413455	20-02-91	WO-A- 9102526	07-03-91
		AT-T- 124040	15-07-95
		CA-A- 2023217	17-02-91
		CA-A- 2127561	17-02-91
		CN-A,B 1049501	27-02-91
		DE-D- 69020262	27-07-95
		DE-T- 69020262	26-10-95
		IL-A- 95331	31-07-95
		JP-A- 7149758	13-06-95
		JP-A- 3086875	11-04-91
		JP-B- 7002734	18-01-95
		PL-B- 166381	31-05-95
		US-A- 5266569	30-11-93
		US-A- 5164402	17-11-92
		US-A- 5229396	20-07-93